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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/556,038	11/09/95	BOUSSIOTIS	V	RPI-022CP

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1642	11

HM31/0303

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DATE MAILED: 03/03/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/8/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 48-101 is/are pending in the application.
Of the above, claim(s) 49-70, 75-76, 91-92, 99-101 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 48, 71-74, 77-90, 93-98 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948 SEE NOTE
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

DETAILED ACTION

1. Effective 2/7/98, the location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1642, Technology Center 1600.

2. Applicant's election with traverse of Group II in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the generic claim 48 drawn to a method of modulating unresponsiveness by a T cells with an agent which modulates a signal associated with ligation of the cytokine receptor γ chain such that unresponsiveness by the T cell is modulated. This is not found persuasive because of the reasons of record set forth in the previous Restriction Requirement (Paper No. 7). As applicant acknowledges in their response, the modulation can result either in T cell stimulation or in T cell inhibition. These are clearly opposite endpoints. Therefore, the claims are drawn to distinct and independent inventions in that the claims are drawn to either stimulating T cell proliferation or to inhibit (induce unresponsiveness) T cell responsiveness.

The requirement is still deemed proper and is therefore made FINAL. JMS 3/2/98

Claims 48 and 71-74, 77-90 and 93-98 are being acted upon as the elected invention.

Non-elected claims 49 -70, 75-76, 91-92 and 99-101 are held to be withdrawn from further consideration under 37 CFR 1.142(b).

Claims 1-47 have been canceled previously.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. This application has been filed with informal drawings which are acceptable for examination purposes only.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6 The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 48 and 71-98 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Applicant has not disclosed how to use cytokine receptor γ chain-specific antibodies to inhibit T cells therapeutically commensurate in scope with claimed methods. There is insufficient information or nexus of the invention with respect to the in vivo ability of cytokine receptor γ chain-specific antibodies to inhibit T cell responsiveness, particularly in vivo, to use applicant's invention.

Applicant's disclosure does not provide any objective evidence of either in vitro, ex vivo or in vivo inhibition of T cell responses with cytokine receptor γ chain-specific antibodies. Further, it is noted that the non-elected claims recite using cytokine receptor γ chain-specific antibodies to achieve the opposite effect of stimulating T cells.

It is noted that the instant inventor has disclose that the same or similar description disclosed in the instant specification provides some evidence that after T cell receptor signaling, an event mediated through the γ_c prevents the induction of anergic state, yet this analysis only helps to begin to decipher the molecular mechanisms associated with T cell anergy (Boussiotis et al. Science, 1994; 1449, #AJ; see last paragraph).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the disclosure as filed accurately reflects the relative efficacy of the claimed therapeutic strategies.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Bach (TIPS, 1993) discloses the art known limitations of treating autoimmune diseases and clearly indicates that autoimmune disease cannot be considered as a whole and treatment selection must be considered with each disease (page 213, column 3). Bach also reviews the art-known resistance of autoimmunity to therapeutic intervention (page 215, column 3).

In addition, it is noted that applicant's methods encompass targeting both acute and chronic inflammatory conditions. Although in vitro experiments and animal models can validate concepts based on studies of human disease, such studies are limited to the acute as opposed to the chronic nature of the disease. For example, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, reliance on the examples of experimental protocols wherein cytokine receptor γ chain-specific antibodies administered at the same time as an inflammatory stimulus may inhibit T cell responses (e.g. acute graft rejection); such results may not reflect targeting those chronic diseases (e.g. autoimmunity, allergy) encompassed by the claimed methods. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens under controlled conditions than that experienced in the human immunoregulatory diseases targeted by the claimed invention. Again, no objective evidence of inhibitory cytokine receptor γ chain-specific antibodies in systems predictive of the therapeutic methods encompassed by the claimed invention has been presented.

It is noted that applicant's disclosure relies, in part, on observations with inhibiting via the B7:CD28 costimulatory pathway (pages 14-17 for the instant specification). In this context, Blazar et al. (J. Immunol., 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10). More, important it is unlikely that ongoing T cell responses will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases or allergies. Therefore, it appears that the administration of inhibitors of the CD28-B7 pathway such as CTLA-4 Ig can result in immunosuppression as observed in several model systems, however even in these systems the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention. There is insufficient evidence on the tissue distribution, half-life, affinity and avidity of cytokine receptor γ chain-specific antibodies as inhibitory reagents in vivo or in vitro.

On the basis of the disclosure alone and in the absence of objective evidence of predictive assays; applicant concludes that cytokine receptor γ chain-specific antibodies can be administered to effectively prevent or treat any antibody-mediated disease in vivo, including human diseases. The specification does not adequately teach how to effectively inhibit T cell responses encompassing organ transplantation, autoimmunity and allergy encompassed by the claimed invention (see pages IV. Therapeutic Use of Gamma Chain Inhibitory Agents on pages 14-17 of the instant specification).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based and/or antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell responses with inhibitory cytokine receptor γ chain-specific antibodies, commensurate in scope with the claimed invention.

8. Claim 48 and 98 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48 and 98 are indefinite and ambiguous in the use of "modulating T cell responsiveness" and "such that T cell responsiveness is modulated" in the absence of a clear positive or negative biological effect. Modulation is not appropriate because modulation can occur both in positive and negative directions and applicant elected methods of inhibiting T cell responses. Also, the endpoint of stimulating signals are ambiguous in the absence of what is the intended or desired biological effect.

The amendments must be supported by the specification so as not to add any new matter.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 48, 71-74, 77-90 and 93-98 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Shimamura et al. (U.S. Patent No. 5,582,826) (see entire document).

Shimamura et al. teach the use of cytokine receptor γ chain-specific antibodies as an immunosuppressant medicine effective in preventing the rejection of grafts after transplantation and also in treating inflammatory diseases such as allergic disease and autoimmune diseases (see Summary of the Invention and column 3, paragraph 1). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced cytokine receptor γ chain-specific antibodies to treat the same inflammatory conditions encompassed by the claimed methods. Although the reference is silent about the mechanism of action of cytokine receptor γ chain-specific antibodies such as its effects on JAK3 kinase, the reference clearly teaches the use of the same cytokine receptor γ chain-specific antibodies to inhibit the same T cell response encompassed by the same therapeutic modalities as applicant. Also see Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Although the reference clearly teaches inhibiting T cell responses associated with transplantation, it is silent about allogeneic, xenogeneic and bone marrow cells as well as GVHD, such limitations would have been either anticipated or obvious to the ordinary artisan in the use of T cell inhibitory antibodies, which were commonly used in such therapeutic regimens at the time the invention was made. Similarly, the reference appears to be silent about alloantigen or autoantigen, however such limitations would have been anticipated or obvious in view of inhibiting T cell responses in the treatment of autoimmunity and transplantation at the time the invention was made.

Therefore, the instant claims relying upon inhibiting T cell responses as well as the mechanism of action of inhibitory cytokine receptor γ chain-specific antibodies (claims 71-74, 77-85, 88, and 98) are anticipated by the reference. The use of inhibitory cytokine receptor γ chain-specific antibodies in the treatment of GVHD would either be immediately envisaged in the inhibition of T cell responses in transplantation as taught by the reference or would have been obvious to the ordinary artisan, since the use of such inhibitory antibodies was known and practiced at the time the invention was made (claims 86, 89-97). It is noted that the mechanism of action is recited in these claims associated with bone marrow transplantation (see claims 93-96), however these limitations are met by using the same inhibitory cytokine receptor γ chain-specific antibodies to be used for the same purpose as the claimed invention.

12. Claims 48, 71-74, 77-90 and 93-98 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Sugamura et al. (U.S. Patent No. 5,5705,608) (see entire document).

Sugamura et al. teach the use of cytokine receptor γ chain-specific antibodies as an immunosuppressant medicine effective in preventing the rejection of grafts after transplantation and also in treating inflammatory diseases such as allergic disease and autoimmune diseases (see Summary of the Invention and column 10, line 42 to column 11, lines16, in particular). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced cytokine receptor γ chain-specific antibodies to treat the same inflammatory conditions encompassed by the claimed methods. Although the reference is silent about the mechanism of action of cytokine receptor γ chain-specific antibodies such as its effects on JAK3 kinase, the reference clearly teaches the use of the same cytokine receptor γ chain-specific antibodies to inhibit the same T cell response encompassed by the same therapeutic modalities as applicant. Also see Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Although the reference clearly teaches inhibiting T cell responses associated with transplantation, it is silent about allogeneic, xenogeneic and bone marrow cells as well as GVHD, such limitations would have been either anticipated or obvious to the ordinary artisan in the use of T cell inhibitory antibodies, which were commonly used in such therapeutic regimens at the time the invention was made. Similary, the reference appears to be silent about alloantigen or autoantigen, however such limitations would have been anticipated or obvious in view of inhibiting T cell responses in the treatment of autoimmunity and transplantation at the time the invention was made.

Therefore, the instant claims relying upon inhibiting T cell responses as well as the mechanism of action of inhibitory cytokine receptor γ chain-specific antibodies (claims 71-74, 77-85, 88, and 98) are anticipated by the reference. The use of inhibitory cytokine receptor γ chain-specific antibodies in the treatment of GVHD would either be immediately envisaged in the inhibition of T cell responses in transplantation as taught by the reference or would have been obvious to the ordinary artisan, since the use of such inhibitory antibodies was known and practiced at the time the invention was made (claims 86, 89-97). It is noted that the mechanism of action is recited in these claims associated with bone marrow transplantation (see claims 93-96), however these limitations are met by using the same inhibitory cytokine receptor γ chain-specific antibodies to be used for the same purpose as the claimed invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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March 2, 1998